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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,548	OLSSON ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/20/01, 4/10/02 and 7/2/02*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9 and 37-46* is/are pending in the application.

4a) Of the above claim(s) *41,43 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,37-40,42,44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/5/02*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attatched* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 11/20/01, 4/10/02 and 7/2/02 and Applicant's response filed 9/24/03 are acknowledged and have been entered.

2. Applicant's election with traverse of the invention of Group I and the species erythropoietin receptor (EPOR) as the species of cell surface receptor and oligopeptide SEQ ID NO: 11 as the exogenous compound in Applicant's response filed 9/24/03 is acknowledged. Applicant's amendment filed 9/24/03 was not fully responsive to the communication mailed 3/25/03 because Applicant failed to elect a species of exogenous ligand. However, Applicant has elected erythropoietin (EPO) as the species of exogenous ligand in an interview with Mr. Ted Apple on 2/27/04 (see accompanying Form PTOL-413).

The basis for the traversal is of record in Applicant's response filed 9/24/03. Applicant's arguments have been fully considered but are not persuasive for the following reasons.

There are two criteria for a proper requirement for restriction between patentably distinct inventions:

> (1) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(I)); and
>
> (2) There must be a serious burden on the Examiner if restriction is not required (see MPEP § 803.02 § 806.04(a) - (j), § 808.01(a) and § 808.02). Regarding undue burden, the M.P.E.P. § 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

The inventions of Groups I-IV are distinct for the reasons of record enunciated at item #2 in the restriction requirement mailed 3/25/03. The restriction requirement enunciated in the previous Action mailed 3/25/03 meets this criterion of serious burden since each Group requires a different field of search, for example, the search required for Groups II and IV require a search of methods comprising a contact step in the presence of an exogenous ligand, whereas the search required for Group II comprises a search of methods wherein the level of receptor activation is increased and the search required for Group IV comprises a search of methods wherein the level of receptor activation is decreased. With regard to Applicant's arguments to *In re Weber* on page 2 of Applicant's response, the claims in *In re Weber* were drawn to cyclic diamine derivatives which possess the common property of psychotherapeutic effectiveness, identified by a single generic formula expressed in Markush format.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 41, 43 and 45 (non-elected species of Group I) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

The invention being examined in this application is a method of modulating the activity of a cell surface receptor comprising a contacting step in the absence of exogenous ligand and wherein the level of receptor activation is increased.

Claims 8, 9, 37-40, 42, 44 and 46 are being acted upon presently.

3. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 09/028,937, 08/788,820, 08/701,382 and 08/612,999 and they are disclosed as being continuing applications in the first line of the specification. However, the three latter applications appear to be continuations-in-part. Applicant should amend the first line of the specification to update the relationship of the priority documents and to update the status of the 09/028,937 parent application.

4. The disclosure is objected to because of the following informality:

In the brief description of the drawings for Figure 1, the disclosure (on page 5 at line 16) is "Figures 1A and 1B". However, the Figure 1 has a top and bottom panel that are not labeled A and B.

Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed method of modulating the activity or internalization of a cell surface receptor.

The instant claims encompass a method of modulating (activating) the activity or (inhibiting) internalization of a cell surface receptor, including a type-2 cell surface receptor such as those recited in the instant claims, comprising contacting the said receptor with an exogenous compound that binds an activation sequence on the said receptor, wherein the activation sequence of the said receptor is a segment of the cell surface receptor having at least 10% amino acid sequence identity and has at least 35% sequence similarity with a sequence of the same length from an MHC Class I α1 domain sequence, the said contacting being accomplished in the absence of any exogenous ligand. More specifically, the instant claims encompass a method for binding to and modulating ***any cell surface receptor*** in the case of claims 8 and 9 (including the orphan receptors disclosed on page 19 at lines 12-27 for which no specific function has been associated), to ***any type-2 cell surface receptor*** in the case of claims 37-40, 42, 44 to the recited cell surface receptors in the case of claim 46, comprising using ***any exogenous compound*** including oligopeptides that have the recited sequence identity and similarity to any segment of the same length from an MHC Class I α1 domain that binds to an activation sequence and produces the function of modulating (increasing) a non-specified activity (exclusive of claims 9 and 44) of a receptor (including a type-2 cell surface receptor and/or including inhibiting internalization of the said receptor). There is insufficient disclosure in the specification of a method using said exogenous compound.

The specification discloses (on page 13 at lines 13-16) that "activation sequences" or "internalization sequences" are involved in modulation of receptor responses. The specification further discloses (on page 15 at lines 23-27) that the activation sequences are initially identified by homology to the sequence of an α1-domain of an MHC Class I antigen and (on page 16 at the last 5 lines) that the amino acid sequence of the receptor region of interest, i.e., "the activation sequence" will have at least about 10% or at least about 15-20% sequence identity and at least about 30% or at least about 35%sequence similarity as determined by using the Wisconsin Package, version 8.0-open VMS, Genetics Computer Group. The specification discloses that MHC Class I antigens include human MHC class I antigens and mammalian equivalents thereof, such as Class I antigens of the H-2 locus of mice. The specification discloses examples (on pages 17-19) of peptides having at least about 35% sequence similarity with the sequence of an α1 domain (such as SEQ ID NO: 1 of the instant application which is a 23-mer) of an MHC Class I antigen. The specification further discloses (at the paragraph spanning pages 14 and 15) that the activation sequence is usually not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor. The specification discloses (at the paragraph spanning pages 27 and 28) that an exogenous compound can be any compound not produced endogenously by the cell or organism such as chemical and small organic moieties and the oligopeptides disclosed in the specification.

The specification discloses oligopeptides that have an amino acid sequence *corresponding to* the activation sequence of the extracellular domain of a cell surface receptor, and the specification discloses that "corresponds" means either that the oligopeptide is identical to all or part of the activation sequence, or that the oligopeptide has substantial homology to the activation sequence and may have an amino acid substitutions, deletions or insertions as compared to the activation sequence (page 20 at lines 5-9). There is no recitation in the instant claims 37-40, 42, 44 and 46 that the exogenous compound is an oligopeptide, nor if it was that it have the recited sequence identity and similarity that the activation sequence has; however, if there was such a recitation, for a 23-mer (such as SEQ ID NO: 1) there are at minimum 14^{20} possible oligopeptides which may not function to modulate the corresponding receptor(s).

The recitation of "exogenous compound" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being exogenously added and being capable of modulating the activity or internalization of a cell surface receptor. Nor does the recitation of "cell surface receptor containing an activation sequence". It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the compound has, and if one extends the analysis in the instant case, what the compound does (i.e., it binds to an activation sequence on a cell surface receptor and modulates an undisclosed activity, or it is a receptor of some type, respectively), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of skill in the art would not have recognized that Applicant was in possession of the necessary common attributes or features possessed by the members of the genus.

7. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ***in vitro*** method for modulating the activity of a type-2 receptor containing an activation sequence that is one of the disclosed receptors from which SEQ ID NO: 2-35 are obtained using an exogenous compound that is an oligopeptide that is one of SEQ ID NOS: 2-35, does not reasonably provide enablement for the claimed method of modulating activity of a receptor that comprises any activation sequence (and including wherein said activation sequence has at least 10% amino acid sequence identity and at least 35% sequence similarity with the sequence of an α1-domain sequence of an MHC Class I antigen), nor wherein the receptor is any receptor and the exogenous compound is any exogenous compound, such as chemical and small organic moieties and oligopeptides that are not one of SEQ ID NO: 2-35, nor wherein the method is an in vivo method using any exogenous compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not disclose how to make/and or use the exogenous compounds of the claimed method.

The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass any exogenous compound in the case of instant claims 8, 9, 37-40, 42, 44 and 46 and any receptor in the case of instant claims 8 and 9 (including the orphan receptors disclosed on page 19 at lines 12-27 for which no specific function has been associated) and any type-2 receptor in the case of instant claims 37-40, 42 and 44 and in vivo methods of modulation.

The specification discloses (on page 13 at lines 13-16) that "activation sequences" or "internalization sequences" are involved in modulation of receptor responses. The specification further discloses (on page 15 at lines 23-27) that the activation sequences are initially identified by homology to the sequence of an α1-domain of an MHC Class I antigen and (on page 16 at the last 5 lines) that the amino acid sequence of the receptor region of interest, i.e., "the activation sequence" will have at least about 10% or at least about 15-20% sequence identity and at least about 30% or at least about 35%sequence similarity as determined by using the Wisconsin Package, version 8.0-open VMS, Genetics Computer Group. The specification discloses that MHC Class I antigens include human MHC class I antigens and mammalian equivalents thereof, such as Class I antigens of the H-2 locus of mice. The specification discloses examples (on pages 17-19) of peptides having at least about 35% sequence similarity with the sequence of an α1 domain (such as SEQ ID NO: 1 of the instant application which is a 23-mer) of an MHC Class I antigen. The specification further discloses (at the paragraph

spanning pages 14 and 15) that the activation sequence is usually not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor. The specification discloses (at the paragraph spanning pages 27 and 28) that an exogenous compound can be any compound not produced endogenously by the cell or organism such as chemical and small organic moieties and the oligopeptides disclosed in the specification. The specification discloses oligopeptides which have an amino acid sequence *corresponding to* the activation sequence of the extracellular domain of a cell surface receptor, and the specification discloses that "corresponds" means either that the oligopeptide is identical to all or part of the activation sequence, or that the oligopeptide has substantial homology to the activation sequence and may have an amino acid substitutions, deletions or insertions as compared to the activation sequence (page 20 at lines 5-9). There is no recitation in the instant claims 37-40, 42, 44 and 46 that the exogenous compound is an oligopeptide, nor if it was that it have the recited sequence identity and similarity that the activation sequence has; however, if they did, for a 23-mer (such as SEQ ID NO: 1) there are at minimum 14^{20} possible oligopeptides which may not function to modulate the corresponding receptor(s).

There is no guidance in the specification as to what alterations result in a functional exogenous compound, including an oligopeptide, or which receptors contain an "activation sequence capable of binding an "exogenous compound", other than the oligopeptides SEQ ID NO: 2-35 and the receptors from which they are derived, and further no disclosure of working examples of in vivo modulation. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain functional activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1), it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify exogenous compounds, including amino acid sequences that have functional activity, it would require undue experimentation to make the corresponding sequences.

In addition, in vivo pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the compound may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the compound; (2) the compound may not reach the target area because, i.e. the compound may not be able to cross the mucosa or the compound may be adsorbed by fluids, cells and tissues where the compound has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The enablement provided by the specification is not commensurate with the scope of the claims. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The limitation "wherein said activation sequence is a segment of said cell surface receptor having at least 10% amino acid sequence identity and at least 35% sequence similarity..." do not have support in the parent application 08/612,999. Also, the limitations 'IL-3 through IL-17 receptors, GCS, TPO, prolactin, TCR and CNF receptors' recited in instant claim 46 do not have support in the parent applications 08/612,999, 08/701,382 and 08/788,820. The limitation "cell surface receptor containing an activation sequence" is only disclosed in parent application 09/027,937. (For example, in parent case serial no. 08/788,820 an "inernalization sequence" is disclosed. Therefore, with regard to application of prior art, the instant application with regard to claims 37-40, 42, 44 and 46 are only entitled to priority of the parent application 08/701,382, i.e., 8/22/1996, with regard to claim 46, that of parent application 09/027,937, i.e., 2/24/1998 and with regard to claims 8 and 9, that of parent application 09/027,937, i.e., 2/24/1998.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 8, 9 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/03438 as evidenced by disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater,162 USPQ 541, 550 - 51 (CCPA 1969). With regard to the limitation "activation sequence", the instant specification discloses that the activation sequence is *usually* not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor (paragraph spanning pages 14 and 15).

WO 96/03438 teaches a method of modulating the internalization of a cell surface receptor, i.e., EPOR, containing an activation sequence, comprising binding an exogenous compound, i.e., an antibody, to the receptor in the absence of exogenous ligand which would normally activate the receptor, i.e., EPO. The mAb #71 appears to bind peptide "SE-8" which is amino acid residues 169-198 of the human erythropoietin receptor and SE-8 comprises SEQ ID NO: 11 of the instant application (especially Figure 1, Abstract, page 33, lines 25-31 and page 34, lines 13-14). With regard to instant claim 46, it is an inherent property of said receptor that it contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and that it is a type-2 cell surface receptor as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23. In addition, several other antibodies are used in the method taught by WO 96/03438, although the reference is silent as to the portion(s) of the EPOR they bind. With regard to the limitation "inhibiting internalization", claim 9 is included in this rejection because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

11. Claims 37-40, 42 and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 96/03438 as evidenced by disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater,162 USPQ 541, 550 - 51 (CCPA 1969). With regard to the limitation "activation sequence", the instant specification discloses that the activation sequence is *usually* not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor (paragraph spanning pages 14 and 15).

WO 96/03438 teaches a method of modulating the internalization of a cell surface receptor, i.e., EPOR, containing an activation sequence, comprising binding an exogenous compound, i.e., an antibody, to the receptor and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, i.e., EPO, and the level of receptor activation is increased. The mAb #71 appears to bind peptide "SE-8" which is amino acid residues 169-198 of the human erythropoietin receptor and SE-8 comprises SEQ ID NO: 11 of the instant application (especially Figure 1, Abstract, page 33, lines 25-31 and page 34, lines 13-14). In addition, several other antibodies are used in the method taught by WO 96/03438, although the reference is silent as to the portion(s) of the EPOR they bind.

With regard to instant claims, it is an inherent property of said receptor that it contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and it is an inherent property of the EPOR that it is a type-2 cell surface receptor as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23. Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event" because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. Claims 8, 9 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/05189 (IDS reference) as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

WO 95/05189 teaches a method of modulating the internalization of a cell surface receptor, i.e., various cell surface receptors including typel and type-2 receptors (see entire document), containing an activation sequence, comprising binding an exogenous compound, i.e., various peptides that bind to a receptor and are comparable to polymorphic sequences in the α-1 domain of Class I, and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, and wherein the level of receptor activation is increased and endocytosis, i.e., internalization, is decreased (especially page 10 at lines 17-29, pages 12-20, examples, table 4, claims). With regard to instant claim 46, it is an inherent property of said receptor that it contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and that it is a type-2 cell surface receptor as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

13. Claims 37-40, 42 and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 95/05189 (IDS reference) as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

WO 95/05189 teaches a method of modulating the internalization of a cell surface receptor, i.e., various cell surface receptors including typel and type-2 receptors (see entire document), containing an activation sequence, comprising binding an exogenous compound, i.e., various peptides that bind to a receptor and are comparable to polymorphic sequences in the α-1 domain of Class I, and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, and wherein the level of receptor activation is increased and endocytosis, i.e., internalization, is decreased (especially

page 10 at lines 17-29, pages 12-20, examples, table 4, claims). Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). With regard to instant claims 37-40, 42 and 44, it is an inherent property of said receptor that it contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and that it is a type-2 cell surface receptor as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

14. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Naranda et al (PNAS USA 94: 11692-11697, 10/1997, IDS reference) as evidenced by disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

Naranda et al teach a method of modulating, i.e., inhibiting, the internalization of a cell surface receptor, i.e., the insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1R), containing an activation sequence, comprising binding an exogenous compound, i.e., peptides derived from the α-1 domain of the MHC class I and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, i.e., Insulin or IGF-1, and wherein the level of receptor activation is increased. With regard to instant claims, it is an inherent property of said receptors that they contain an activation sequence as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23. Naranda et al further teach that the said method may be generally applicable to identifying receptor domains that play a role in receptor endocytosis, and that novel compounds that interact with such domains may have therapeutic potential for selectively altering the steady-state number of chosen cell surface receptors, that the α-1 domain peptides can recognize distinctively different sequences among different receptors, those receptors having extracellular domains that are homologous to MHC class I alpha domains, through the interaction of identical or similar sequences (especially last paragraph of article and discussion section on page 11696). Naranda et al teach GHRR and leptin receptor and some other membrane receptors also contain extracellular domains homologous to MHC class I α-1 domains and that their internalization is inhibited selectively by cognate peptides. With regard to instant claims, it is an inherent property of said receptors that they contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and it is an inherent property of the HGHR and leptin receptors that they are type-2 cell surface receptors as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at

lines 1-2 and 22-23. Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event" and with regard to the limitation "inhibiting internalization", claim 9 is included in this rejection because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

15. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,885,574 (IDS reference) as evidenced by WO 96/03438 and by disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater,162 USPQ 541, 550 - 51 (CCPA 1969). With regard to the limitation "activation sequence", the instant specification discloses that the activation sequence is *usually* not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor (paragraph spanning pages 14 and 15).

U.S. Patent No. 5,885,574 discloses a method of modulating the internalization of a cell surface receptor, i.e., EPOR, containing an activation sequence, comprising binding an exogenous compound, i.e., an antibody, to the receptor and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, i.e., EPO, and wherein the level of receptor activation is increased. In addition, several other antibodies are used in the method disclosed by U.S. Patent No. 5,885,574, although the reference is silent as to the portion(s) of the EPOR they bind. With regard to instant claims, it is an inherent property of said receptor that it contains an activation sequence having at least 10% amino acid sequence identity and at least 35% sequence similarity with a segment of the same length from an MHC class I α-1 domain sequence and it is an inherent property of the EPOR that it is a type-2 cell surface receptor as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23. Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event" and with regard to the limitation "inhibiting internalization", claim 9 is included in this rejection because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the

process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). U.S. Patent No. 5,885,574 discloses an oligopeptide "SEQ ID NO: 12" which is from the human erythropoietin receptor. "SEQ ID NO: 12" of '574 comprises SEQ ID NO: 11 of the instant application.

Evidentiary reference WO 96/03438 teaches that the mAb #71 appears to bind among other peptides, peptide "SE-8" which is amino acid residues 169-198 of the human erythropoietin receptor and SE-8 comprises SEQ ID NO: 11 of the instant application (especially Figure 1, Abstract, page 33, lines 25-31 and page 34, lines 13-14). In addition, several other antibodies are used in the method taught by, although the reference is silent as to the portion(s) of the EPOR they bind.

16. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,639,458 (IDS reference).

U.S. Patent No. 5,639,458 discloses a method of modulating the internalization of a cell surface receptor, i.e., various cell surface receptors including type-1 and type-2 receptors (especially column 4 at lines 22-50), containing an activation sequence, comprising binding an exogenous compound, i.e., various peptides that bind to a receptor and are comparable to polymorphic sequences in the α-1 domain of Class I, and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, and wherein the level of receptor activation is increased and endocytosis, i.e., internalization, is decreased (especially Abstract, column 4 at lines 22-50, column 6 at lines 4167, examples, table 4, claims). Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 8, 9, 37-40, 42, 44 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,853,999 (IDS reference).

U.S. Patent No. 5,853,999 discloses a method of modulating the internalization of a cell surface receptor, i.e., various cell surface receptors including type-1 and type-2 receptors (especially column 4 at lines 22-50), containing an activation sequence, comprising binding an exogenous compound, i.e., various peptides that bind to a receptor and are comparable to polymorphic sequences in the α-1 domain of Class I, and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, and wherein the level of receptor activation is increased and endocytosis, i.e., internalization, is decreased (especially Abstract, column 4 at lines 22-50, column 6 at lines

12-22 and 38-67, examples, table 4). Claim 44 is included in this rejection with regard to the limitation "wherein activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event because the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 8, 9, 37-40, 42, 44 and 46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of copending Application No. 10/074,695. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of the '695 application comprising use of an oligopeptide comprising an internalization sequence recited in claim 7 of the '695 application is encompassed by the claimed method of the instant application comprising use of an exogenous compound to modulate the activity or inhibit internalization of a cell surface receptor because the oligopeptide recited in the '695 application is an oligopeptide corresponding to the extracellular domain of a cell surface receptor and the exogenous compound recited in the method of instant claims 37-40, 42, 44 and 46 is an oligopeptide that binds to an activation sequence on the extracellular domain of a cell surface receptor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 8, 9, 37-40, 42, 44 and 46 are directed to an invention not patentably distinct from claim 7 of commonly assigned copending Application No. 10/074,695. Specifically, the method of the '695 application comprising use of an oligopeptide comprising an internalization sequence recited in claim 7 of the '695 application is encompassed by the claimed method of the instant application comprising use of an exogenous compound to modulate the activity or inhibit internalization of a cell surface receptor because the oligopeptide recited in the '695 application is an oligopeptide corresponding to the extracellular domain of a cell surface receptor and the exogenous compound recited in the method of instant claims 37-40, 42, 44 and 46 is an oligopeptide that binds to an activation sequence on the extracellular domain of a cell surface receptor.

21. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned Application No. 10/074,695, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

22. It is noted by the Examiner that reference #12 on Applicant's IDS filed 8/5/02 is drawn to the subject that does not appear to be related to the subject matter of the instant application, i.e., to a printhead for ink jet printing.

23. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

24. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y. Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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